



## **The patient perspective: quality of life in advanced heart failure with frequent hospitalisations**

Nieminen, Markku S ; Dickstein, Kenneth ; Fonseca, Cândida ; Serrano, Jose Magaña ; Parissis, John ; Fedele, Francesco ; Wikström, Gerhard ; Agostoni, Piergiuseppe ; Atar, Shaul ; Baholli, Loant ; Brito, Dulce ; Colet, Josep Comín ; Édes, István ; Gómez Mesa, Juan E ; Gorjup, Vojka ; Garza, Eduardo Herrera ; González Juanatey, José R ; Karanovic, Nenad ; Karavidas, Apostolos ; Katsytadze, Igor ; Kivikko, Matti ; Matskeplishvili, Simon ; Merkely, Béla ; Morandi, Fabrizio ; Novoa, Angel ; Oliva, Fabrizio ; Ostadal, Petr ; Pereira-Barretto, Antonio ; Pollesello, Piero ; Rudiger, Alain ; Schwinger, Robert H G ; Wieser, Manfred ; Yavelov, Igor ; Zymliński, Robert

**Abstract:** End of life is an unfortunate but inevitable phase of the heart failure patients' journey. It is often preceded by a stage in the progression of heart failure defined as advanced heart failure, and characterised by poor quality of life and frequent hospitalisations. In clinical practice, the efficacy of treatments for advanced heart failure is often assessed by parameters such as clinical status, haemodynamics, neuro-hormonal status, and echo/MRI indices. From the patients' perspective, however, quality-of-life-related parameters, such as functional capacity, exercise performance, psychological status, and frequency of re-hospitalisations, are more significant. The effects of therapies and interventions on these parameters are, however, underrepresented in clinical trials targeted to assess advanced heart failure treatment efficacy, and data are overall scarce. This is possibly due to a non-universal definition of the quality-of-life-related endpoints, and to the difficult standardisation of the data collection. These uncertainties also lead to difficulties in handling trade-off decisions between quality of life and survival by patients, families and healthcare providers. A panel of 34 experts in the field of cardiology and intensive cardiac care from 21 countries around the world convened for reviewing the existing data on quality-of-life in patients with advanced heart failure, discussing and reaching a consensus on the validity and significance of quality-of-life assessment methods. Gaps in routine care and research, which should be addressed, were identified. Finally, published data on the effects of current i.v. vasoactive therapies such as inotropes, inodilators, and vasodilators on quality-of-life in advanced heart failure patients were analysed.

DOI: <https://doi.org/10.1016/j.ijcard.2015.04.235>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-115520>

Journal Article

Published Version

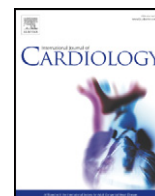


The following work is licensed under a Creative Commons: Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.

Originally published at:

Nieminen, Markku S; Dickstein, Kenneth; Fonseca, Cândida; Serrano, Jose Magaña; Parissis, John; Fedele, Francesco; Wikström, Gerhard; Agostoni, Piergiuseppe; Atar, Shaul; Baholli, Loant; Brito, Dulce; Colet, Josep Comín; Édes, István; Gómez Mesa, Juan E; Gorjup, Vojka; Garza, Eduardo Herrera; González Juanatey, José R; Karanovic, Nenad; Karavidas, Apostolos; Katsytadze, Igor; Kivikko, Matti; Matskeplishvili, Simon; Merkely, Béla; Morandi, Fabrizio; Novoa, Angel; Oliva, Fabrizio; Ostadal, Petr; Pereira-Barretto, Antonio; Pollesello, Piero; Rudiger, Alain; Schwinger, Robert H G; Wieser, Manfred; Yavelov, Igor; Zymliński, Robert (2015). The patient perspective: quality of life in advanced heart failure with frequent hospitalisations. *International Journal of Cardiology*, 191:256-264.

DOI: <https://doi.org/10.1016/j.ijcard.2015.04.235>



## Review

# The patient perspective: Quality of life in advanced heart failure with frequent hospitalisations



Markku S. Nieminen <sup>a,\*</sup>, Kenneth Dickstein <sup>b</sup>, Cândida Fonseca <sup>c</sup>, Jose Magaña Serrano <sup>d</sup>, John Parissis <sup>e</sup>, Francesco Fedele <sup>f</sup>, Gerhard Wikström <sup>g</sup>, Piergiuseppe Agostoni <sup>h</sup>, Shaul Atar <sup>i</sup>, Loant Baholli <sup>j</sup>, Dulce Brito <sup>k</sup>, Josep Comín Colet <sup>l</sup>, István Édes <sup>m</sup>, Juan E. Gómez Mesa <sup>n</sup>, Vojka Gorjup <sup>o</sup>, Eduardo Herrera Garza <sup>p</sup>, José R. González Juanatey <sup>q</sup>, Nenad Karanovic <sup>r</sup>, Apostolos Karavidas <sup>s</sup>, Igor Katsytadze <sup>t</sup>, Matti Kivikko <sup>u</sup>, Simon Matskeplishvili <sup>v</sup>, Béla Merkely <sup>w</sup>, Fabrizio Morandi <sup>x</sup>, Angel Novoa <sup>y</sup>, Fabrizio Oliva <sup>z</sup>, Petr Ostadal <sup>aa</sup>, Antonio Pereira-Barretto <sup>ab</sup>, Piero Pollesello <sup>u</sup>, Alain Rudiger <sup>ac</sup>, Robert H.G. Schwinger <sup>ad</sup>, Manfred Wieser <sup>ae</sup>, Igor Yavelov <sup>af</sup>, Robert Zymliński <sup>ag</sup>

<sup>a</sup> Helsinki University Central Hospital, Helsinki, Finland

<sup>b</sup> University of Bergen, Stavanger University Hospital, Norway

<sup>c</sup> S. Francisco Xavier Hospital, CHLO, NOVA Medical School, Faculdade de Ciências Médicas, Universidade Nova de Lisboa, Portugal

<sup>d</sup> División de Educación en Salud, UMAE Hospital de Cardiología Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Mexico

<sup>e</sup> Second University Cardiology Clinic, Attiko Teaching Hospital, Athens, Greece

<sup>f</sup> Department of Cardiovascular, Respiratory, Nephrology and Geriatric Science, University of Rome, Italy

<sup>g</sup> Department of Cardiology, Akademiska Hospital, Uppsala, Sweden

<sup>h</sup> Critical Cardiology Department, Centro Cardiologico Monzino, Milan, Italy

<sup>i</sup> Department of Cardiology, Galilee Medical Center, Nahariya, Israel

<sup>j</sup> Department of Intensive Care, Klinikum Dortmund, Germany

<sup>k</sup> Cardiology Department, Hospital Universitario de Santa Maria, Lisbon, Portugal

<sup>l</sup> IMIM Hospital del Mar Medical Research Institute, Barcelona, Spain

<sup>m</sup> Department of Cardiology, University of Debrecen, Hungary

<sup>n</sup> Fundación Valle del Lili, Cali, Colombia

<sup>o</sup> Department of Intensive Internal Medicine, University Medical Center Ljubljana, Slovenia

<sup>p</sup> Heart Failure, Heart Transplant Department, Centro Médico Zambrano Hellion, Heart Failure Clinic Unidad Médica de Alta Especialidad, Hospital de Cardiología No. 34, IMSS Monterrey Nuevo León, Mexico

<sup>q</sup> Cardiology and Coronary Care Department, Clinico Santiago de Compostela, Spain

<sup>r</sup> Clinical Department of Anaesthesiology and Intensive Care, University Hospital of Split, Croatia

<sup>s</sup> Heart Failure Clinic & Echo Lab, Gennimatas General Hospital of Athens, Greece

<sup>t</sup> Cardiology Intensive Care Unit, O. Bogomolets National Medical University, Kiev, Ukraine

<sup>u</sup> Critical Care, Orion Pharma, Espoo, Finland

<sup>v</sup> Bakulev Scientific Center for Cardiovascular Surgery, Moscow, Russia

<sup>w</sup> Heart and Vascular Center, Semmelweis University, Budapest, Hungary

<sup>x</sup> Department of Cardiovascular Science, University of Insubria, Circolo Hospital and Macchi Foundation, Varese, Italy

<sup>y</sup> Clínica El Rosario, Medellín, Colombia

<sup>z</sup> Department of Cardiology, Niguarda Ca'Granda Hospital, Milan, Italy

<sup>aa</sup> Department of Cardiology, Cardiovascular Center, Na Homolce Hospital, Prague, Czech Republic

<sup>ab</sup> Hospital das Clínicas da Faculdade de Medicina, University of São Paulo, Brazil

<sup>ac</sup> Institute of Anaesthesiology, University Hospital Zurich, Switzerland

<sup>ad</sup> Department of Internal Medicine, Kliniken Nordoberpfalz, Weiden, Germany; Teaching Hospital of the University of Regensburg, Germany

<sup>ae</sup> Department of Internal Medicine 1, University Hospital Krems, Karl Landsteiner University of Health Sciences, Austria

<sup>af</sup> Scientific Research Institute of Physico-Chemical Medicine of the Federal Medico-Biological Agency of the Russian Federation, Moscow, Russia

<sup>ag</sup> Department of Cardiology, Cardiology Intensive Care Unit, The 4th Military Hospital, Wrocław, Poland

\* Corresponding author.

E-mail address: [markku.nieminen@hus.fi](mailto:markku.nieminen@hus.fi) (M.S. Nieminen).

## ARTICLE INFO

## Article history:

Received 1 April 2015

Accepted 30 April 2015

Available online 1 May 2015

## Keywords:

Advanced heart failure

Quality of life

Trade-off

Levosimendan

Nitroprusside

Nesiritide

## ABSTRACT

End of life is an unfortunate but inevitable phase of the heart failure patients' journey. It is often preceded by a stage in the progression of heart failure defined as advanced heart failure, and characterised by poor quality of life and frequent hospitalisations. In clinical practice, the efficacy of treatments for advanced heart failure is often assessed by parameters such as clinical status, haemodynamics, neurohormonal status, and echo/MRI indices. From the patients' perspective, however, quality-of-life-related parameters, such as functional capacity, exercise performance, psychological status, and frequency of re-hospitalisations, are more significant. The effects of therapies and interventions on these parameters are, however, underrepresented in clinical trials targeted to assess advanced heart failure treatment efficacy, and data are overall scarce. This is possibly due to a non-universal definition of the quality-of-life-related endpoints, and to the difficult standardisation of the data collection. These uncertainties also lead to difficulties in handling trade-off decisions between quality of life and survival by patients, families and healthcare providers. A panel of 34 experts in the field of cardiology and intensive cardiac care from 21 countries around the world convened for reviewing the existing data on quality-of-life in patients with advanced heart failure, discussing and reaching a consensus on the validity and significance of quality-of-life assessment methods. Gaps in routine care and research, which should be addressed, were identified. Finally, published data on the effects of current i.v. vasoactive therapies such as inotropes, inodilators, and vasodilators on quality-of-life in advanced heart failure patients were analysed.

© 2015 The Authors. Published by Elsevier Ireland Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Introduction

Advanced heart failure (AdHF) is a malignant disease by nature [1]. It is characterised by a debilitating late course, with increasingly frequent hospitalisations and considerable morbidity besides the obvious mortality [2]. Heart failure affects quality of life (QoL) more profoundly than many other chronic diseases [3]. Even though QoL is a major concern, it appears that clinical management as well as research efforts do not focus sufficiently on this aspect. There is no good universal understanding of QoL in clinical practice [4]. Moreover, clinical trials often lack the assessment of relevant parameters, let alone using them as endpoints. Methods used are often subjective nonparametric measures either by patient or treating physician. In AdHF, daily variation is high and challenging for statistical analysis. Changes in echocardiographic or laboratory parameters indeed represent quantifiable outcomes, but they do not necessarily improve the daily life of the study participants, which is related to variables less easy to be quantified, such as self-care [5]. Also, QoL is by itself frequently variable in heart failure patients experience sometimes for reasons independent from the clinical conditions of the patient.

Treatment generally aims at reducing mortality, but longevity might well be an overrated goal in the management of AdHF. If the patient has to choose between prolongation of life and maintaining acceptable QoL, the choice is not always obvious. For example, some patients might decide against the implantation of an implantable cardiac defibrillator (ICD), even though they know that this choice can shorten their survival [6, 7], when sudden death is foreseen as the most desirable outcome. Also, decisions can change over time, depending on the feelings of the patients and their families. As yet, there is only little data to shed light on this trade-off.

Finally, when AdHF patients experience a decompensation and are hospitalised they often receive, on top of the optimal treatment with ACEi/ARB,  $\beta$ -blockers, and aldosterone-antagonist, some i.v. vasoactive treatment, i.e. inotropes, inodilators, and vasodilators. There seems to be scarce evidence on the effect of these i.v. treatments for hospitalised AdHF patients on short- or long-term QoL.

A panel of 34 experts in the field of cardiology, intensive care medicine, and cardiovascular pharmacology from 21 countries (Austria, Brazil, Colombia, Croatia, Czech Republic, Finland, Germany, Greece, Hungary, Israel, Italy, Mexico, Norway, Poland, Portugal, Russia, Slovenia, Spain, Sweden, Switzerland, and Ukraine) convened in Munich on January 23, 2015 for reviewing the existing data on QoL in patients with AdHF, and for discussing and reaching a consensus on the validity and significance of QoL assessment methods. Gaps in routine care and research, which should be addressed, were identified. Finally, published data on the effect of non-pharmacologic and pharmacologic treatments on QoL in AdHF patients were analysed.

## 2. Definition of QoL

QoL is not well defined in chronic heart failure and even less so in acute heart failure. None of the guidelines specify this outcome. Apparently, some aspects such as depression and social function disability, which are shown to have a significant impact on health-related QoL in patients with heart failure [8], are not taken into consideration to a satisfying degree. Other factors affecting QoL and functionality comprise persistent congestion, neurohormonal/inflammatory activation, reduced peripheral muscle blood flow/myopathy, reduced kidney function, and right ventricular dysfunction, along with severely compromised haemodynamic state, which lead to cachexia. The inflammatory activation present in heart failure has been shown to correlate with QoL [9]. Moreover, QoL decreases as New York Heart Association (NYHA) functional class worsens [10]. Finally, exercise intolerance is a key factor.

Most of the available quality-of-life scores, such as the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and the Kansas City Cardiomyopathy Questionnaire (KCCQ), are related to three major dimensions: physical, emotional, and social. Indeed, the data on available treatments commonly relate to the effects of therapy on these dimensions, but they are often rendered as the overall QoL scores without a thorough discussion of the individual domains.

## 3. Assessment of QoL

Besides objective surrogate measurements, various subjective methods can be used to assess the QoL in patients with heart failure, depending on whether their condition is acute or chronic (Table 1). A pilot study suggests that health-related quality-of-life measures can be reliably collected using internet-based software [11]. Data collected in this manner are valid and of comparable quality to self-reported data

**Table 1**  
Current methods to assess the QoL in acute and chronic heart failure.

Acute heart failure
• Visual analogue scale
• Likert scale (both by patient or physician)
• Surrogate measures of dyspnoea index, BNP levels, lung function according to peak expiratory flow measures, and others.
Chronic heart failure
• Web-based possibilities to ask patients how they feel (questionnaires)
• Standard questionnaire: Minnesota living with heart failure (MLHF)
• Standard questionnaire: Kansas city cardiomyopathy questionnaire (KCCQ)
• 6 min walking test is also used as an indicator of QoL or quality of performance
• New York Heart Association functional class
• RAND-36 general health survey (computer-based, requires the patient to be able to use the system)

obtained via paper survey. Further validation and development is needed. Assessment methods of QoL in acute and advanced chronic heart failure vary because of the time-frame factor: e.g. short term ameliorations in dyspnea are one of the typical parameters followed in patients hospitalised for acute heart failure [12], while the walking test is considered of importance in advanced heart failure patients.

### 3.1. QoL assessment in acute heart failure

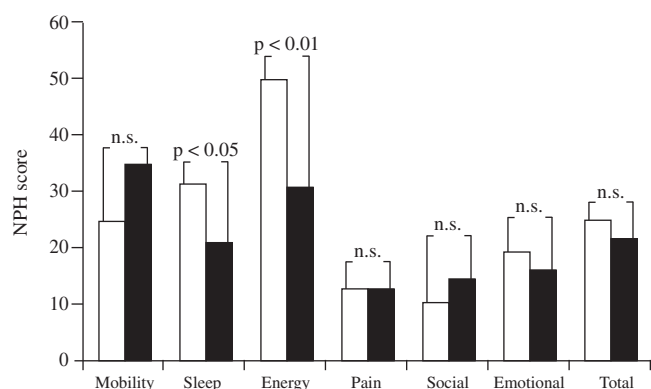
While the visual analogue scale (VAS) offers absolute assessment of symptoms such as dyspnoea (endpoint: AUC over 5 days), the Likert scale focuses on relative assessment (endpoint: moderate/marked improvement at 6, 12, and 24 h) [13]. These scales have been used widely in acute heart failure trials. However, benefits conferred by the treatment are often hard to demonstrate. A commendable approach might be the inclusion of patients in studies early on, followed by monitoring of their changes in dyspnoea over time.

In the acute setting, symptoms such as congestion and clinical assessment of other heart failure signs are crucial, as they will also define the patient's QoL after hospital discharge. There is a consensus that, after hospital stay, patients should be followed up not only in terms of their disease trajectory, but also concerning their QoL. Dyspnoea scores in the acute phase and self-reported outcomes after one month of discharge are recommended as the instruments of choice. In the acute setting, dyspnoea is a compromised measure as it is subjective and hampered by hospital environment, extra administration of oxygen, infections, poor lung function and even positioning of the patient in bed rest. Dyspnoea scores as an index parameter should be evaluated as early as possible during hospitalisation as a parametric measure of therapeutic efficacy.

Due to its significance for adverse events and treatment compliance, depression is an important aspect. However, there are no reliable tools available to estimate depression in the acute phase. Many of the instruments are based on self-rated questionnaires, while the diagnostic gold standard is actually the interview with the specialist. Mental state is affected by the degree of dyspnea, congestion and even hyponatremia, when present [14].

### 3.2. QoL assessment in chronic heart failure

In a pivotal study assessing the impact of AdHF on QoL in 79 patients hospitalised with HF in Sweden, patients were found to be significantly more affected by detrimental effects on sleep and energy than patients with stroke, as measured with the Nottingham Health Profile (NHP) (Fig. 1) [15]. Both ESC and AHA highlighted the importance of patient



**Fig. 1.** QoL in patients with HF and stroke in the acute phase, measured by NHP (from Franzén-Dahlin [15]). Higher scores indicate greater number and severity of problems HF: heart failure; NHP: Nottingham Health Profile; NS: not significant; QoL: quality of life. White bars: heart failure patients (n = 77); black bars: aphasic stroke patients (n = 56).

reported outcomes in heart failure by publishing recently two recommendations at this regard [16, 17].

In chronic heart failure, the MLHFQ and the KCCQ are standard assessment instruments, with the KCCQ being the most popular for use in clinical studies. There are some differences between these two that are elucidated in Table 2 [18].

The KCCQ, followed by the NYHA classification and the 6-minute walk test, was found to reflect clinical changes in patients with heart failure most accurately [19]. Correlation coefficients for social, functional and physical areas are higher with the KCCQ than with the MLHFQ. Moreover, a more precise correlation of the KCCQ with survival has been established [9].

These scores have some limitations, however. For instance, reduced functional capacity is not sufficiently covered by the KCCQ. The NYHA classification might also be less than optimal, because it was developed in 1970s in patients that differed from today's typical population.

Apart from questionnaires, when surrogate measures are called for, exercise capacity can be evaluated by the use of the 6-minute walk test or the cardiopulmonary exercise test. The latter is more accurate and reproducible than the 6-minute walk test, but less practical for everyday use. Finally, psychological distress is a high risk in this vulnerable patient group [20]. A holistic test that explores the physical, psychological and social aspects alike is the assessment of the patient's sexual satisfaction [21].

## 4. Rehospitalisation

While mortality neither reflects disease burden nor disease progression, because heart failure progresses stepwise, rehospitalisation rate is a comprehensive measure of these outcomes. The length of hospital stays has generally decreased over time in heart failure patients, but re-admission rates have essentially remained unchanged [22]. After discharge, approximately 50% of all patients are readmitted within six months. Re-hospitalisation within 30 days occurs in 25% of cases. The readmission rate increases from initial discharge to death with a high ratio of preventable readmissions in the initial phase [23]. As Fig. 2 shows, the risk for readmission is highest immediately following discharge and just before death.

### 4.1. Rehospitalisation as a measure of QoL

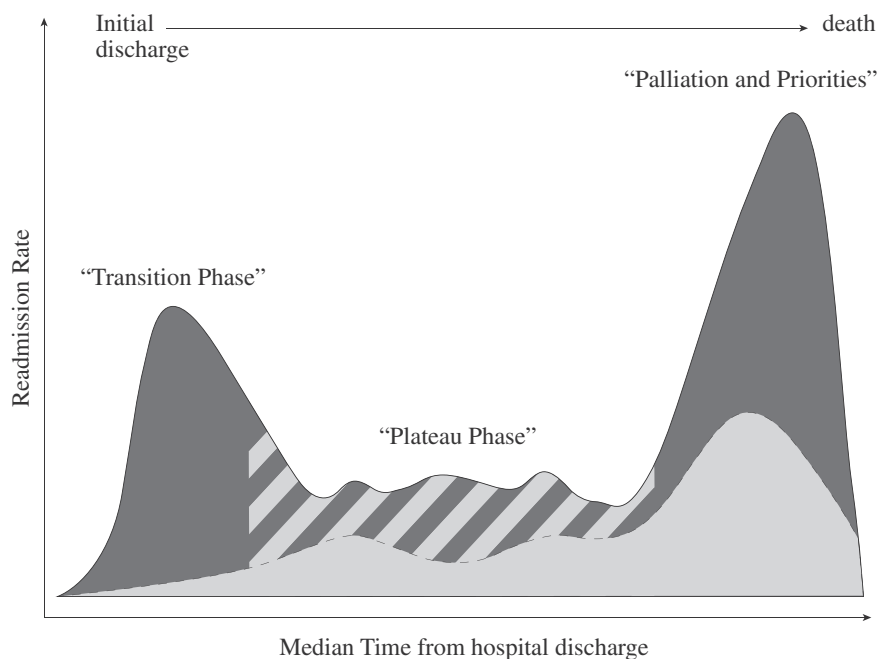
Congestion is the most frequent cause of readmission. Other factors associated with increased risk of readmission include higher age, comorbidities, premature discharge and noncompliance. Hospitalisation satisfies the demands of true surrogate endpoints, but it is also an endpoint in itself. It is easy to identify and easy to quantify. Time to first hospitalisation, frequency of hospitalisations, and duration of hospital admissions can be assessed. Another dimension that matters from the patient's point of view could be the number of days out of hospital as a possible interpretation of QoL.

**Table 2**

Comparison between the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and the Kansas City Cardiomyopathy Questionnaire (KCCQ).

From Rector [18].

MLHFQ	KCCQ
Self-administered	Self-administered
21 items	23 items
Chronic heart failure-related physical, emotional and social aspects	Functional score: physical activity and symptoms
	Summary score: functional score plus QoL
	Specific dimensions: "self-efficacy" & "social limitation"
Each question, 6 point Likert scale	Each question, 5–7 point Likert scale
Total range, 0–105	Total range, 0–100
The higher, the worse	The higher, the better



**Fig. 2.** Lifetime readmission risk after heart failure hospitalisation. Dark grey areas: highest risk for readmission; striped areas: lower risk, plateau phase; light grey area: assumed baseline of inevitable readmissions.

From Desai & Stevenson [23].

Early readmission is associated with worse long-term outcomes and significant increases in heart-failure-related health costs. With each readmission, QoL declines [24]. However, the established questionnaires of QoL hardly assess hospitalisation frequency.

#### 4.2. Rehospitalisation as a measure of quality of care

At the same time, readmissions can be perceived as a parameter of quality of care. Hospitals frequently fail to implement strategies commonly recommended to reduce rehospitalisation [25]. Heart failure admission rates were demonstrated to vary considerably between institutions [26]. Readmission, however, is not necessarily a sign of failure, as higher rates could be a consequence of successful care. Patients who die during their index episodes can, in fact, never be readmitted [27]. Also, some elective readmissions for enhancement of medical care or interventions, including implantable device therapies, may represent appropriate care that reduces mortality.

#### 4.3. HF management programmes

Improved outcomes have been achieved in outpatients discharged from the emergency department with early collaborative care (care provided by a primary care physician and a cardiologist) [28]. Patient management in multidisciplinary heart failure treatment centres that includes remote monitoring and self-treatment at home is deemed capable of lowering readmission rates [23]. As rehospitalisation often occurs early, the panel feels that re-evaluation of the patient by the heart failure nursing staff or the treating physicians in the first two weeks after discharge would be important.

Several strategies are associated with lower risk-standardised 30-day readmission rates (RSRR): [29]

- Partnering with community physicians or physician groups to reduce readmission;
- Partnering with local hospitals to reduce readmissions;
- Having nurses responsible for medication reconciliation;
- Arranging follow-up appointments before discharge;

- Having a process in place to send all discharge papers or electronic summaries directly to the patient's primary physician;
- Assigning staff to follow up on test results that return after the patient is discharged.

The number of selected strategies implemented was found to correlate with the RSRR.

#### 5. The role of therapy in the improvement of QoL

Treatment goals naturally differ according to the setting. In acute heart failure, survival is considered predominant over QoL due to the irreversibility of death. In this line, the panel feels that more efficacious interventions for decongestion and improvement of haemodynamic measures are needed, as the hospitalisation rates remain high. However, even in the acute setting, several aspects of QoL, such as depression, deserve heightened attention and should not be neglected, as mental state may be a significant factor for treatment compliance. More research is required on the effects of acute heart failure therapies on QoL.

Depression is certainly one of the most important factors determining QoL in heart failure patients [8]. Its prevalence in acute and chronic heart failure is estimated at 35% to 60% and 11% to 25%, respectively [30]. An OPTIMIZE-HF analysis revealed that history of depression is a predictor of length of hospital stay and post-discharge mortality [31].

Previous studies have suggested that their use can be associated with an increased likelihood of death and cardiovascular hospitalisation due to adverse pharmacodynamics effects [32]. Because depression has also been shown to be associated with increased mortality in these patients, it remains unclear if this association is due to the use of antidepressants or to depression [33].

Special attention regarding the quality-of-life issues is required in the "palliative setting". Palliative care is by definition meant for malignant states with known short life expectancy. It is commendable in AdHF patients to prefer the term of "end-of-life" care. As opposed to the management of cancer patients, the length of this stage is hard to predict in the heart failure setting, particularly with current traditional



HF classifications by NYHA classification and the ACC/AHA staging. In fact, conventional nosology for the staging of heart failure has a number of limitations, among which the inaccuracy in predicting the “end-of-life” heart failure stages [34]. As well known, heart failure per se is not confined to the heart, but it is a multiple-organ disease [35]. A new staging system for heart failure, named HLM, has been proposed [36, 37], which could be useful in assessing the true “end-of-life” stage heart failure patients in order to apply palliative care and to enhance QoL of these individuals.

We should be more accurate in identifying HF patients with signs of multi organ failure in the early phase of the disease, during re-hospitalisations and during outpatients follow-up. Early organ protection and organ support in AdHF (liver, kidney, central nervous system) is of the outmost importance for early and/or more appropriate treatment or for identifying patients needing cyclic hospital treatment to improve HF condition and QoL.

## 6. Pharmacological therapy

Medical treatment aiming at improving haemodynamic and QoL-related outcomes such as congestion, cardiac output, cardiac index, right ventricular failure in hospitalised AdHF patients are described in the literature. When AdHF patients experience a decompensation and are hospitalised they often receive, on top of the optimal treatment with ACEi/ARB,  $\beta$ -blockers, and aldosterone-antagonist, some i.v. vasoactive treatment, i.e. inotropes, inodilators, and vasodilators. According to the AHA/ACC guidelines [38], inotropes and vasodilators are viable pharmacological options for advanced chronic heart failure. The effects of intermittent or repetitive doses of inotropes, vasodilators and inodilators in AdHF patients have been described, both for a mere palliative aim and also as a bridge to transplant. Their effects on surrogate endpoints related to QoL have been also described, albeit with big gaps for important parameters such as depression (Table 3). We hereby review the documented effects of established inotropes, inodilators, and vasodilators on QoL-related parameters in AdHF patients.

### 6.1. Dobutamine

Dobutamine has been used in chronic or repetitive fashion on patients with AdHF [42]. However, it was documented that dobutamine causes tachyphylaxis [43], and its use in heart failure has been associated with increased mortality [44]. In a comparison of dobutamine-based and milrinone-based therapy for advanced decompensated congestive heart failure, dobutamine was considered more attractive also due to a better economic impact [45].

### 6.2. Milrinone

Continuous intravenous milrinone therapy has been administered at home in selected patients with advanced heart failure who are listed for transplant [46]. Some evidence was collected on the fact that this phosphodiesterase inhibitor reduces the number of hospitalisations and decreases the overall treatment costs of acute heart failure [47]. However, despite its beneficial haemodynamic actions, long-term therapy with oral milrinone was shown to increase the morbidity and mortality of patients with severe chronic heart failure [48]. Also the Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study does not support the routine use of intravenous milrinone as an adjunct to standard therapy in the treatment of patients hospitalised for an exacerbation of chronic heart failure [49].

### 6.3. Levosimendan

Recent systematic reviews and meta-analyses reported that the calcium sensitizer levosimendan conveys benefits that are relevant for the patient's QoL [50, 51]. In a study by Parissis et al., functional capacity and scores of emotional stress favoured levosimendan over placebo [52]. Trials assessing the effects of repetitive administration have yielded improvements regarding functional capacity, left ventricular ejection fraction, and quality-of-life scores [53–55]. Potential explanations for these effects relate to levosimendan-mediated, sustained reductions in inflammatory cytokines and apoptotic factors [56, 57]. Furthermore, levosimendan treatment decreases oxidative stress, prevents oxidative damage, and improves endothelial function as well as right ventricular function [58–60]. Improving of right ventricular function is especially important in AdHF with signs of right ventricular failure since ascites, oedema and liver or kidney dysfunction have an important impact on QoL. Brain natriuretic peptide (BNP) levels and inflammatory markers are reduced in comparison to placebo [61]. In the REVIVE II trial an improvement in dyspnoea by levosimendan as compared to placebo was shown [62]. In the LevoRep trial, the effects of repetitive levosimendan infusions on 6-minute walk test, KCCQ clinical summary score, and event-free survival were described [63]. In a recent comparison with dobutamine, levosimendan significantly reduced re-hospitalisation rates and shortened the length of hospital stay in acute heart failure by 1.5 days [64, 65].

### 6.4. Nitroprusside

Nitroprusside was shown to be more effective than dobutamine in patients with end-stage heart failure awaiting heart transplantation [42]. In patients with advanced, low-output heart failure, vasodilatory

**Table 3**  
Effects of inotropic and vasoactive therapies currently used in clinical practice on outcomes in AdHF patients.

	Hemodynamics		Neuro-hormons	QoL-related parameters			Survival
	Cardiac index	Congestion/PCWP		Dyspnoea	Rehospitali-zation rate	Depression	
Dobutamine	↑↑	↓	↓	↓	↑ <sup>b</sup>	n.d.	↓ <sup>g</sup>
Milrinone	↑↑	↓↓	↔	↓	↔ <sup>c</sup>	n.d.	↓ <sup>h</sup>
Levosimendan	↑↑	↓↓	↓	↓	↓ <sup>b</sup>	↓ <sup>f</sup>	↑ <sup>b,i</sup>
Nitroprusside	↑ <sup>a</sup>	↓↓	↓	↓	↔ <sup>d</sup>	n.d.	↑ <sup>c</sup>
Nesiritide	↑ <sup>a</sup>	↓↓	↓	↓	↔ <sup>e</sup>	n.d.	↔ <sup>j</sup>

n.d. = no relevant data obtained by cross-searching PubMed for (“parameter” and “active compound”[ti]).

<sup>a</sup> Indirect effect.

<sup>b</sup> According to Fedele et al. [64].

<sup>c</sup> According to Lewis et al. [39].

<sup>d</sup> According to Mullens et al. [40].

<sup>e</sup> According to O'Connor et al. [41].

<sup>f</sup> According to Parissis et al. [52].

<sup>g</sup> According to Capomolla et al. [42] (vs. nitroprusside).

<sup>h</sup> According to Packer et al. [48].

<sup>i</sup> According to the meta-analyses by Nieminen et al. [50] and Silvetti et al. [51].

<sup>j</sup> According to Reed et al. [68].

therapy with sodium nitroprusside used in conjunction with optimal current medical therapy during hospitalisation might be associated with favourable long-term clinical outcomes [40].

### 6.5. Nesiritide

The effects of nesiritide on mortality and quality of life of AdHF patients were studied in the two FUSION clinical trials [66, 67], which gave promising but not definitive answers, the authors warranting for a definitive phase III mortality/quality of life trial. In the ASCEND-HF trial, it did not significantly influence medical resource use or health utilities compared with standard care alone [68].

### 6.6. Drugs under development

Data on the effect on QoL parameters by the treatment of AdHF patients with vasodilators under clinical development such as carperitide, serelaxin, and ularitide have been also published in the literature.

Carperitide was also used intermittently in outpatients with AdHF. However, the experience is very limited here [69].

Serelaxin, a vasoactive peptide hormone, was shown to give rise to a significant but clinically small improvement in dyspnoea over placebo according to the VAS scale, but not according to the Likert scale in the RELAX-AHF trial [70]. The 180-day mortality was slightly but significantly reduced. A sub-analysis revealed that benefits for both Likert and VAS dyspnoea evaluation are seen in patients with preserved left ventricular ejection fraction [71].

Ularitide, a synthetic natriuretic peptide hormone, is also capable of improving dyspnoea and BNP levels [72]. A currently ongoing phase 3, randomised, double-blind, placebo-controlled study in patients with acute heart failure will provide additional 6 month morbidity and mortality evidence.

## 7. Non-pharmacological therapy

Physical training is an important component of heart failure management, even if the severity of the disease creates limitation in the adherence of patients to exercise programmes [73, 74].

Further, devices such as biventricular pacemakers for cardiac resynchronisation therapy (CRT) and mitral clips for severe mitral insufficiency could always be considered in appropriate heart failure patients. In fact, AdHF patients often experience atrial fibrillation, which necessitates expert care on heart rate control [75]. More recent advancements were reviewed elsewhere [76].

Although CRT-P that enhances QoL should be maintained, at the end-of-life ICDs frequently deliver multiple shocks, which is a matter of anxiety and poor QoL for patients and carers, and should be deactivated [77, 78].

Further, tele-monitoring of patients discharged after heart failure exacerbation is an important addition and was shown to be cost-effective [79]. Finally, non-compliance with non-pharmacological recommendations in heart failure patients, was clearly associated with adverse outcome [80].

## 8. Trade-off survival vs. QoL

Postponing death is a treatment goal apart from symptom relief. Under certain circumstances, however, if life-prolonging measures are expected to impair QoL, a choice has to be made between these two. Recently, Eschaler and co-workers tried to give an answer to the question if there is any benefit in optimising heart failure treatment in over-80 year-old patients with their study HF-80 [81]. Several trials investigated the topic of end-life-preferences in heart failure patients, with conflicting results [7]. While preferences remained in favour of survival for many patients despite AdHF symptoms in the study by Stevenson et al. [82], Kraai et al. found that the majority of patients attach more

weight to QoL over longevity [6]. Another trial identified two distinct groups of patients, one preferring treatments that prolonged survival time and another that favoured strategies that improved QoL but reduced survival time [7]. These treatment preferences were independent of functional or symptomatic status, suggesting that they may be decided early in the course of illness. Formiga et al. stated that advance planning of end-of-life procedures and doctor–patient communication regarding these items remain poor and must be improved [83]. Finally, heart failure patients' own requests to forego resuscitation should be considered. Dev et al. stated that these requests may reflect preferences for intervention to enhance quality rather than prolong survival, which is particularly important as these patients have high early mortality [84].

## 9. Future research with focus on QoL

The inclusion of QoL or QoL-related parameters as clear primary endpoint in future trials is strongly advocated. An important aspect that should be elucidated is risk stratification that allows for the ideal timing of patient discharge from hospital in order to avoid early readmission. Also, validation of simple instruments such as the VAS would be called for to facilitate their use in clinical practice. Up to date, there are few but promising studies evaluating the safety and efficacy of antidepressants in acute heart failure [85]. Future trials are also required to assess the utility of treatments for depression and their safety profiles. This is of growing importance considering the advancing average age of heart failure patients, in whom drug–drug interactions and compliance issues pose a challenge.

## 10. Conclusion

Heart failure adversely affects QoL, and its deterioration appears to be related to poor long-term prognosis. QoL is influenced by a multitude of factors derived from the physical, emotional and social situation of the patient, which is why it cannot be categorised easily. Comprehensive team approaches are of uppermost priority for many patients and their relatives/caregivers, particularly in the end-of-life setting.

It appears that the available instruments of assessment require refinement with the aim of greater practicability in daily routine. Also, QoL is frequently missing as an endpoint in clinical studies on AdHF patients, even though it doubtlessly offers merits as a measure of efficacy of treatment.

An issue which has not been debated well enough in the literature or in the clinical societies is the trade-off of survival vs QoL. It still seems a taboo to admit that very often this is a matter of choice for patients, families, and doctors, and that survival is not the clear answer [6, 7]. It remains therefore puzzling that demonstrating advantages on long term survival for new drugs to be used in the acute phase of AdHF is still a requirement in regulatory clinical trials, while improvement of QoL are not.

However, we are comforted by a recent report by Pani and co-workers [86] where methods are advocated for the validation of patient reported outcomes and measurements of well-being. We agree also with those authors that the evaluation of 'real-life' treatment effectiveness and of health as a value would help in the development of drugs which take into account the "patient-perspective".

In hospital drug therapy as well as non-pharmacological out-of-hospital strategies should be adjusted according to QoL goals. In this way it should be possible to also prevent unplanned frequent readmissions, which are a common burden in the end-of-life stage of patients with AdHF. Finally, the panel went through the sparse and controversial evidence on the effects on QoL of i.v. inotropes and vasodilators used during hospitalisation of AdHF patients. Among the drugs already used in clinical practice, encouraging advantages were reported in the literature for the inodilator levosimendan. Promising vasodilators such as serelaxin and ularitide could also prove useful in the near future.



## Author contributions

Three of the authors (MSN, MK, PP) independently performed the preliminary search for the relevant publications. All of the authors contributed substantially to discussions of the existing literature and to the text of the recommendations, and reviewed the manuscript before submission.

## Declaration of interest

This project did not receive any financial support, apart for covering the logistic expenses related to the organisation of the consensus meeting in Munich on January 23, 2015, which was achieved by collecting unrestricted educational grants from Orion Pharma (Finland), AbbVie (U.S.A.), Medis d.o.o. (Slovenia) and Biomed JR Ltd. (Israel). The attendees did not receive any honoraria. PP and MK are employees of Orion Pharma.

## Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

## Acknowledgments

We thank Drs. Judith Moser for editing of the manuscript.

## References

- [1] T. Jaarsma, J.M. Beattie, M. Ryder, F.H. Rutten, T. McDonagh, P. Mohacsi, S.A. Murray, T. Grodzicki, I. Bergh, M. Metra, I. Ekman, C. Angermann, M. Leventhal, A. Pitsis, S.D. Anker, A. Gavazzi, P. Ponikowski, K. Dickstein, E. Delacretaz, L. Blue, F. Strasser, J. McMurray, Advanced Heart Failure Study Group of the HFA of the ESC, Palliative care in heart failure: a position statement from the palliative care workshop of the Heart Failure Association of the European Society of Cardiology, *Eur. J. Heart Fail.* 11 (2009) 433–443.
- [2] S.C. Ahluwalia, C.P. Gross, S.I. Chaudhry, Y.M. Ning, L. Leo-Summers, P.H. Van Ness, T.R. Fried, Impact of comorbidity on mortality among older persons with advanced heart failure, *J. Gen. Intern. Med.* 27 (2012) 513–519.
- [3] T. Jaarsma, P. Johansson, S. Agren, A. Strömberg, Quality of life and symptoms of depression in advanced heart failure patients and their partners, *Curr. Opin. Support. Palliat. Care* 4 (2010) 233–237.
- [4] K. Sauser, J.A. Spertus, L. Pierchala, E. Davis, P.S. Pang, Quality of life assessment for acute heart failure patients from emergency department presentation through 30 days after discharge: a pilot study with the Kansas City Cardiomyopathy Questionnaire, *J. Card. Fail.* 20 (2014) 378.e11–5.
- [5] H.G. Buck, C.S. Lee, D.K. Moser, N.M. Albert, T. Lennie, B. Bentley, L. Worrall-Carter, B. Riegel, Relationship between self-care and health-related quality of life in older adults with moderate to advanced heart failure, *J. Cardiovasc. Nurs.* 27 (2012) 8–15.
- [6] I.H. Kraai, K.M. Vermeulen, M.L. Luttik, T. Hoekstra, T. Jaarsma, H.L. Hillege, Preferences of heart failure patients in daily clinical practice: QoL or longevity? *Eur. J. Heart Fail.* 15 (2013) 1113–1121.
- [7] J. MacIver, V. Rao, D.H. Delgado, N. Desai, J. Ivanov, S. Abbey, H.J. Ross, Choices: a study of preferences for end-of-life treatments in patients with advanced heart failure, *J. Heart Lung Transplant.* 27 (2008) 1002–1007.
- [8] M. Schowalter, G. Gelbrich, S. Störk, J.P. Langguth, C. Morbach, G. Ertl, H. Fallner, C.E. Angermann, Generic and disease-specific health-related QoL in patients with chronic systolic heart failure: impact of depression, *Clin. Res. Cardiol.* 102 (2013) 269–278.
- [9] J.T. Parissis, M. Nikolaou, D. Farmakis, I.A. Paraskevaidis, V. Bistola, K. Venetsanou, D. Katsaras, G. Filippatos, D.T. Kremastinos, Self-assessment of health status is associated with inflammatory activation and predicts long-term outcomes in chronic heart failure, *Eur. J. Heart Fail.* 11 (2009) 163–169.
- [10] J. Juenger, D. Schellberg, S. Kraemer, A. Haunstetter, C. Zugck, W. Herzog, M. Haass, Health related QoL in patients with congestive heart failure: comparison with other chronic diseases and relation to functional variables, *Heart* 87 (2002) 235–241.
- [11] B.D. Bliven, S.E. Kaufman, J.A. Spertus, Electronic collection of health-related QoL data: validity, time benefits, and patient preference, *Qual. Life Res.* 10 (2001) 15–22.
- [12] R.L. West, A.F. Hernandez, C.M. O'Connor, R.C. Starling, R.M. Califf, A review of dyspnea in acute heart failure syndromes, *Am. Heart J.* 160 (2010) 209–214.
- [13] J.R. Teerlink, M. Metra, G.M. Felker, P. Ponikowski, A.A. Voors, B.D. Weatherley, A. Marmor, A. Katz, J. Gryzbowski, E. Unemori, S.L. Teichman, G. Cotter, Relaxin for the treatment of patients with acute heart failure (Pre-RELAX-AHF): a multicenter, randomized, placebo-controlled, parallel-group, dose-finding phase IIb study, *Lancet* 373 (2009) 1429–1439.
- [14] L. Shavit, I. Mikeladze, C. Torem, I. Slotki, Mild hyponatremia is associated with functional and cognitive decline in chronic hemodialysis patients, *Clin. Nephrol.* 82 (2014) 313–319.
- [15] A. Franzén-Dahlin, M.R. Karlsson, M. Mejhert, A.C. Laska, Quality of life in chronic disease: a comparison between patients with heart failure and patients with aphasia after stroke, *J. Clin. Nurs.* 19 (2010) 1855–1860.
- [16] S.D. Anker, S. Agewall, M. Borggrefe, M. Calvert, J. Jaime Caro, M.R. Cowie, I. Ford, J.A. Paty, J.P. Riley, K. Swedberg, L. Tavazzi, I. Wiklund, P. Kirchhof, The importance of patient-reported outcomes: a call for their comprehensive integration in cardiovascular clinical trials, *Eur. Heart J.* 35 (2014) 2001–2009.
- [17] J.S. Rumsfeld, K.P. Alexander, D.C. Goff Jr., M.M. Graham, P.M. Ho, F.A. Masoudi, D.K. Moser, V.L. Roger, M.S. Slaughter, K.G. Smolderen, J.A. Spertus, M.D. Sullivan, D. Treat-Jacobson, J.J. Zerwic, American Heart Association Council on Quality of Care and Outcomes Research, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease, and Stroke Council, Cardiovascular Health: the importance of measuring patient-reported health status: a scientific statement from the American Heart Association, *Circulation* 127 (2013) 2233–2249.
- [18] T. Rector, M.T. Olivari, T.B. Levine, G.S. Francis, J.N. Cohn, Predicting survival for an individual with congestive heart failure using the plasma norepinephrine concentration, *Am. Heart J.* 114 (1 Pt 1) (1987) 148–152.
- [19] J.A. Spertus, E. Peterson, M.W. Conard, P.A. Heidenreich, H.M. Krumholz, P. Jones, P.A. McCullough, I. Pina, J. Tooley, W.S. Weintraub, J.S. Rumsfeld, Cardiovascular Outcomes Research Consortium, Monitoring clinical changes in patients with heart failure: a comparison of methods, *Am. Heart J.* 150 (2005) 707–715.
- [20] D.S. Yu, D.T. Lee, J. Woo, D.R. Thompson, Correlates of psychological distress in elderly patients with congestive heart failure, *J. Psychosom. Res.* 57 (2004) 573–581.
- [21] T. Hoekstra, I. Lesman-Leegte, M.L. Luttik, R. Sanderma, D.J. van Veldhuisen, T. Jaarsma, Sexual problems in elderly male and female patients with heart failure, *Heart* 98 (2012) 1647–1652.
- [22] M. Gheorghiade, M. Vaduganathan, G.C. Fonarow, R.O. Bonow, Rehospitalization for heart failure: problems and perspectives, *J. Am. Coll. Cardiol.* 61 (2013) 391–403.
- [23] A.S. Desai, L.W. Stevenson, Rehospitalization for heart failure: predict or prevent? *Circulation* 126 (2012) 501–506.
- [24] R.M. Mills, The heart failure frequent flyer: an urban legend, *Clin. Cardiol.* 32 (2009) 67–68.
- [25] E. Bradley, H. Sipsma, L. Curry, D. Mehrotra, L.I. Horwitz, H. Krumholz, Quality collaboratives and campaigns to reduce readmissions: what strategies are hospitals using? *J. Hosp. Med.* 8 (2013) 601–608.
- [26] R.S. Bhatia, P.C. Austin, T.A. Stukel, M.J. Schull, A. Chong, J.V. Tu, D.S. Lee, Outcomes in patients with heart failure treated in hospitals with varying admission rates: population-based cohort study, *BMJ Qual. Saf.* 23 (2014) 981–988.
- [27] E.Z. Gorodeski, R.C. Starling, E.H. Blackstone, Are all readmissions bad readmissions? *N. Engl. J. Med.* 363 (2010) 297–298.
- [28] D.S. Lee, T.A. Stukel, P.C. Austin, D.A. Alter, M.J. Schull, J.J. You, A. Chong, D. Henry, J.V. Tu, Improved outcomes with early collaborative care of ambulatory heart failure patients discharged from the emergency department, *Circulation* 122 (2010) 1806–1814.
- [29] E. Bradley, L. Curry, L.I. Horwitz, H. Sipsma, Y. Wang, M.N. Walsh, D. Goldmann, N. White, L.L. Piña, H.M. Krumholz, Hospital strategies associated with 30-day readmission rates for patients with heart failure, *Circ. Cardiovasc. Qual. Outcomes* 6 (2013) 444–450.
- [30] G. Gnanasekaran, Epidemiology of depression in heart failure, *Heart Fail. Clin.* 7 (2011) 1–10.
- [31] N.M. Albert, G.C. Fonarow, W.T. Abraham, M. Gheorghiade, B.H. Greenberg, E. Nunez, C.M. O'Connor, W.G. Stough, C.W. Yancy, J.B. Young, Depression and clinical outcomes in heart failure: an OPTIMIZE-HF analysis, *Am. J. Med.* 122 (2009) 366–373.
- [32] A. Sherwood, J.A. Blumenthal, R. Trivedi, K.S. Johnson, C.M. O'Connor, K.F. Adams Jr., C.S. Dupree, R.A. Waugh, D.R. Bensimhon, L. Gauden, R.H. Christenson, G.G. Koch, A.L. Hinderliter, Relationship of depression to death and hospitalization in patients with heart failure, *Arch. Intern. Med.* 167 (2007) 367–373.
- [33] C.M. O'Connor, W. Jiang, M. Kuchibhatla, R.H. Mehta, G.L. Clary, M.S. Cuffe, E.J. Christopher, J.D. Alexander, R.M. Califf, R.R. Krishnan, Antidepressant use, depression, and survival in patients with heart failure, *Arch. Intern. Med.* 168 (2008) 2232–2237.
- [34] P. Moons, K. Van Deyk, W. Budts, The NYHA classification, employment, and physical activities are poor indicators of quality of life after congenital cardiac surgery, *Ann. Thorac. Surg.* 82 (2006) 1167–1168.
- [35] S. Neubauer, The failing heart — an engine out of fuel, *N. Engl. J. Med.* 356 (2007) 1140–1151.
- [36] F. Fedele, P. Severino, S. Calcagno, M. Mancone, Heart failure: TNM-like classification, *J. Am. Coll. Cardiol.* 63 (2014) 1959–1960.
- [37] F. Fedele, M.C. Gatto, A. D'Ambrosi, M. Mancone, TNM-like classification: a new proposed method for heart failure staging, *ScientificWorldJournal* 2013 (2013) 175925.
- [38] C.W. Yancy, M. Jessup, B. Bozkurt, J. Butler, D.E. Casey Jr., M.H. Drazner, G.C. Fonarow, S.A. Geraci, T. Horwich, J.L. Januzzi, M.R. Johnson, E.K. Kasper, W.C. Levy, F.A. Masoudi, P.E. McBride, J.J. McMurray, J.E. Mitchell, P.N. Peterson, B. Riegel, F. Sam, L.W. Stevenson, W.H. Tang, E.J. Tsai, B.L. Wilkoff, American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines, *Circulation* 128 (2013) e240–e327.
- [39] D.A. Lewis, N.R. Gurram, W.T. Abraham, W.S. Akers, Effect of nesiritide versus milrinone in the treatment of acute decompensated heart failure, *Am. J. Health Syst. Pharm.* 60 (Suppl. 4) (2003) S16–S20.

- [40] W. Mullens, Z. Abrahams, G.S. Francis, H.N. Skouri, R.C. Starling, J.B. Young, D.O. Taylor, W.H. Tang, Sodium nitroprusside for advanced low-output heart failure, *J. Am. Coll. Cardiol.* 52 (2008) 200–207.
- [41] C.M. O'Connor, R.C. Starling, A.F. Hernandez, P.W. Armstrong, K. Dickstein, V. Hasselblad, G.M. Heizer, M. Komajda, B.M. Massie, J.J. McMurray, M.S. Nieminen, C.J. Reist, J.L. Rouleau, K. Swedberg, K.F. Adams Jr., S.D. Anker, D. Atar, A. Battler, R. Botero, N.R. Bohidar, J. Butler, N. Clausell, R. Corbalán, M.R. Costanzo, U. Dahlstrom, L.I. Deckelbaum, R. Diaz, M.E. Dunlap, J.A. Ezekowitz, D. Feldman, G.M. Felker, G.C. Fonarow, D. Gennevois, S.S. Gottlieb, J.A. Hill, J.E. Hollander, J.G. Howlett, M.P. Hudson, R.D. Kociol, H. Krum, A. Laucevicius, W.C. Levy, G.F. Méndez, M. Metra, S. Mittal, B.H. Oh, N.L. Pereira, P. Ponikowski, W.H. Tang, S. Tanomsp, J.R. Teerlink, F. Triposkiadis, R.W. Troughton, A.A. Voors, D.J. Whellan, F. Zannad, R.M. Califf, Effect of nesiritide in patients with acute decompensated heart failure, *N. Engl. J. Med.* 365 (2011) 32–43.
- [42] S. Capomolla, O. Febo, C. Opasich, G. Guazzotti, A. Caporotondi, M.T. La Rovere, M. Gnemmi, A. Mortara, M. Vona, G.D. Pinna, R. Maestri, F. Cobelli, Chronic infusion of dobutamine and nitroprusside in patients with end-stage heart failure awaiting heart transplantation: safety and clinical outcome, *Eur. J. Heart Fail.* 3 (2001) 601–610.
- [43] P. Gibelin, P. Bossan, E. Ferrari, M. Drici, P. Morand, Treatment of chronic heart insufficiency with dobutamine. Value and limitations, *Presse Med.* 21 (1992) 1680–1684.
- [44] C.L. Tacon, J. McCaffrey, A. Delaney, Dobutamine for patients with severe heart failure: a systemic review and meta-analysis of randomised controlled trials, *Intensive Care Med.* 38 (2012) 359–367.
- [45] M.H. Yamani, S.A. Haji, R.C. Starling, L. Kelly, N. Albert, D.L. Knack, J.B. Young, Comparison of dobutamine-based and milrinone-based therapy for advanced decompensated congestive heart failure; hemodynamic efficacy, clinical outcome, and economic impact, *Am. Heart J.* 142 (2001) 998–1002.
- [46] S.C. Brozena, C. Twomey, L.R. Goldberg, S.S. Desai, B. Drachman, A. Kao, E. Popjes, R. Zimmer, M. Jessup, A prospective study of continuous intravenous milrinone therapy for status IB patients awaiting heart transplant at home, *J. Heart Lung Transplant.* 23 (2004) 1082–1086.
- [47] J.E. Boger, S.L. DeLuca, D.F. Watkins, K.K. Vershave, A.M. Thomley, Infusion therapy with milrinone in the home care setting for patients who have advanced heart failure, *J. Intraven. Nurs.* 20 (1997) 148–154.
- [48] M. Packer, J.R. Carver, R.J. Rodeheffer, R.J. Ivanhoe, R. DiBianco, S.M. Zeldis, G.H. Hendrix, W.J. Bommer, U. Elkayam, M.L. Kukin, et al., Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group, *N. Engl. J. Med.* 325 (1991) 1468–1475.
- [49] M.S. Cuffe, R.M. Califf, K.F. Adams Jr., R. Benza, R. Bourge, W.S. Colucci, B.M. Massie, C.M. O'Connor, I. Pina, R. Quigg, M.A. Silver, M. Gheorghiade, Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) Investigators, Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial, *JAMA* 287 (2002) 1541–1547.
- [50] M.S. Nieminen, J. Altenberger, T. Ben-Gal, A. Böhrer, J. Comin-Colet, K. Dickstein, I. Edes, F. Fedele, C. Fonseca, M.J. García-González, G. Giannakoulas, Z. Iakobishvili, P. Jääskeläinen, A. Karavidas, J. Kettner, M. Kivikko, L.H. Lund, S.T. Matskeplishvili, M. Metra, F. Morandi, F. Oliva, A. Parkhomenko, J. Parissis, P. Pollesello, G. Pözl, R.H. Schwinger, J. Segovia, M. Seidel, B. Vrtovc, G. Wikström, Repetitive use of levosimendan for treatment of chronic advanced heart failure: clinical evidence, practical considerations, and perspectives: an expert panel consensus, *Int. J. Cardiol.* 174 (2014) 360–367.
- [51] S. Silvestri, T. Greco, A.L. Di Prima, M. Mucchetti, C.M. de Lurdes, L. Pasin, M. Scandroglio, G. Landoni, A. Zangrillo, Intermittent levosimendan improves mid-term survival in chronic heart failure patients: meta-analysis of randomised trials, *Clin. Res. Cardiol.* 103 (2014) 505–513.
- [52] J.T. Parissis, C. Papadopoulos, M. Nikolaou, V. Bistola, D. Farmakis, I. Paraskevaidis, G. Filippatos, D. Kremastinos, Effects of levosimendan on QoL and emotional stress in advanced heart failure patients, *Cardiovasc. Drugs Ther.* 21 (2007) 263–268.
- [53] S. Mavrogeni, G. Giamouzis, E. Papadopolou, S. Thomopoulou, A. Dritsas, G. Athanasopoulos, E. Adreanides, I. Vassiliadis, K. Spargias, D. Panagiotakos, D.V. Cokkino, A 6-month follow-up of intermittent levosimendan administration effect on systolic function, specific activity questionnaire, and arrhythmia in advanced heart failure, *J. Card. Fail.* 13 (2007) 556–559.
- [54] E.F. Papadopolou, S.I. Mavrogeni, A. Dritsas, D.V. Cokkino, Assessment of QoL using three activity questionnaires in heart failure patients after monthly, intermittent administration of levosimendan during a six-month period, *Hellenic J. Cardiol.* 50 (2009) 269–274.
- [55] N.M. Parle, M.D. Thomas, L. Dembo, M. Best, G.O. Driscoll, Repeated infusions of levosimendan: well tolerated and improves functional capacity in decompensated heart failure – a single-centre experience, *Heart Lung Circ.* 17 (2008) 206–210.
- [56] J.T. Parissis, S. Adamopoulos, C. Antoniadis, G. Kostakis, A. Rigas, S. Kyrzopoulos, E. Iliodromitis, D. Kremastinos, Effects of levosimendan on circulating pro-inflammatory cytokines and soluble apoptosis mediators in patients with decompensated advanced heart failure, *Am. J. Cardiol.* 93 (2004) 1309–1312.
- [57] A. Trikas, C. Antoniadis, G. Latsios, K. Vassiliadou, I. Karamitros, D. Tousoulis, C. Tentolouris, C. Stefanadis, Long-term effects of levosimendan infusion on inflammatory processes and sFas in patients with severe heart failure, *Eur. J. Heart Fail.* 8 (2006) 804–809.
- [58] J.T. Parissis, I. Andreadou, S.L. Markantonis, V. Bistola, A. Louka, A. Pyriochou, I. Paraskevaidis, G. Filippatos, E.K. Iliodromitis, D.T. Kremastinos, Effects of levosimendan on circulating markers of oxidative and nitrosative stress in patients with advanced heart failure, *Atherosclerosis* 195 (2007) e210–e215.
- [59] J.T. Parissis, A. Karavidas, V. Bistola, S. Arapi, I.A. Paraskevaidis, D. Farmakis, D. Korres, G. Filippatos, E. Matsakas, D.T. Kremastinos, Effects of levosimendan on flow-mediated vasodilation and soluble adhesion molecules in patients with advanced chronic heart failure, *Atherosclerosis* 197 (2008) 278–282.
- [60] J.T. Parissis, I. Paraskevaidis, V. Bistola, D. Farmakis, F. Panou, K. Kourea, M. Nikolaou, G. Filippatos, D. Kremastinos, Effects of levosimendan on right ventricular function in patients with advanced heart failure, *Am. J. Cardiol.* 98 (2006) 1489–1492.
- [61] J.T. Parissis, S. Adamopoulos, D. Farmakis, G. Filippatos, I. Paraskevaidis, F. Panou, E. Iliodromitis, D.T. Kremastinos, Effects of serial levosimendan infusions on left ventricular performance and plasma biomarkers of myocardial injury and neurohormonal and immune activation in patients with advanced heart failure, *Heart* 92 (2006) 1768–1772.
- [62] M. Packer, W. Colucci, L. Fisher, B.M. Massie, J.R. Teerlink, J. Young, R.J. Padley, R. Thakkar, L. Delgado-Herrera, J. Salon, C. Garratt, B. Huang, T. Saraphojja, REVIVE Heart Failure Study Group, Effect of levosimendan on the short-term clinical course of patients with acutely decompensated heart failure, *J. Am. Coll. Cardiol. Heart Fail.* 1 (2013) 103–111.
- [63] J. Altenberger, J.T. Parissis, A. Costard-Jaeckle, A. Winter, C. Ebner, A. Karavidas, K. Sihorsch, E. Avgeropoulou, T. Weber, L. Dimopoulos, H. Ulmer, G. Poelzl, Efficacy and safety of the pulsed infusions of levosimendan in outpatients with advanced heart failure (LevoRep) study: a multicentre randomized trial, *Eur. J. Heart Fail.* 16 (2014) 898–906.
- [64] F. Fedele, A. D'Ambrosi, N. Bruno, C. Caira, B. Brasolin, M. Mancone, Cost-effectiveness of levosimendan in patients with acute heart failure, *J. Cardiovasc. Pharmacol.* 58 (2011) 363–366.
- [65] C. Lucioni, A. D'Ambrosi, S. Mazzi, P. Pollesello, M. Apajasalo, F. Fedele, Economic evaluation of levosimendan versus dobutamine for the treatment of acute heart failure in Italy, *Adv. Ther.* 29 (2012) 1037–1050.
- [66] C.W. Yancy, M.T. Saltzberg, R.L. Berkowitz, B. Bertolet, K. Vijayaraghavan, K. Burnham, R.M. Oren, K. Walker, D.P. Horton, M.A. Silver, Safety and feasibility of using serial infusions of nesiritide for heart failure in an outpatient setting (from the FUSION I trial), *Am. J. Cardiol.* 94 (2004) 595–601.
- [67] C.W. Yancy, H. Krum, B.M. Massie, M.A. Silver, L.W. Stevenson, M. Cheng, S.S. Kim, R. Evans, FUSION II Investigators, The Second Follow-up Serial Infusions of Nesiritide (FUSION II) trial for advanced heart failure: study rationale and design, *Am. Heart J.* 153 (2007) 478–484.
- [68] S.D. Reed, P. Kaul, Y. Li, Z.J. Eapen, L. Davidson-Ray, K.A. Schulman, B.M. Massie, P.W. Armstrong, R.C. Starling, C.M. O'Connor, A.F. Hernandez, R.M. Califf, Medical resource use, costs, and quality of life in patients with acute decompensated heart failure: findings from ASCEND-HF, *J. Card. Fail.* 19 (2013) 611–620.
- [69] K. Nishi, Y. Sato, T. Miyamoto, M. Toma, R. Taniguchi, R. Fukuhara, S. Saijo, H. Fujiwara, Y. Takatsu, Intermittent infusions of carperitide or inotropes in outpatients with advanced heart failure, *J. Cardiol.* 59 (2012) 366–373.
- [70] J.R. Teerlink, G. Cotter, B.A. Davison, G.M. Felker, G. Filippatos, B.H. Greenberg, P. Ponikowski, E. Unemori, A.A. Voors, K.F. Adams Jr., M.I. Dorobantu, L.R. Grinfeld, G. Jondeau, A. Marmor, J. Masip, P.S. Pang, K. Werdan, S.L. Teichman, A. Trapani, C.A. Bush, R. Saini, C. Schumacher, T.M. Severin, M. Metra, RELAXin in Acute Heart Failure (RELAX-AHF) Investigators, Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial, *Lancet* 381 (2013) 29–39.
- [71] G. Filippatos, J.R. Teerlink, D. Farmakis, G. Cotter, B.A. Davison, G.M. Felker, B.H. Greenberg, T. Hua, P. Ponikowski, T. Severin, E. Unemori, A.A. Voors, M. Metra, Serelaxin in acute heart failure patients with preserved left ventricular ejection fraction: results from the RELAX-AHF trial, *Eur. Heart J.* 35 (2013) 1041–1050.
- [72] V. Mitrovic, P.M. Seferovic, D. Simeunovic, A.D. Ristic, M. Miric, V.S. Moiseyev, Z. Kobalava, K. Nitsche, W.G. Forssmann, H. Lüss, M. Meyer, Haemodynamic and clinical effects of ulatride in decompensated heart failure, *Eur. Heart J.* 27 (2006) 2823–2832.
- [73] V.M. Conraads, C. Deaton, E. Piotrowski, N. Santaularia, S. Tierney, M.F. Piepoli, B. Pieske, J.P. Schmid, K. Dickstein, P.P. Ponikowski, T. Jaarsma, Adherence of heart failure patients to exercise: barriers and possible solutions: a position statement of the Study Group on Exercise Training in Heart Failure of the Heart Failure Association of the European Society of Cardiology, *Eur. J. Heart Fail.* 14 (2012) 451–458.
- [74] C.M. O'Connor, D.J. Whellan, K.L. Lee, S.J. Keteyian, L.S. Cooper, S.J. Ellis, E.S. Leifer, W.E. Kraus, D.W. Kitzman, J.A. Blumenthal, D.S. Rendall, N.H. Miller, J.L. Fleg, K.A. Schulman, R.S. McKelvie, F. Zannad, I.L. Piña, HF-ACTION Investigators, Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial, *JAMA* 301 (2009) 1439–1450.
- [75] D.R. Warriner, P.J. Sheridan, End-stage heart failure non-pharmacological therapy: recent advances in pacemakers, pressure monitors, pumps and other devices, *Postgrad. Med. J.* 90 (2014) 164–170.
- [76] W.T. Abraham, G.M. De Ferrari, Novel non-pharmacological approaches to heart failure, *J. Cardiovasc. Transl. Res.* 7 (2014) 263–265.
- [77] R. Lampert, D.L. Hayes, G.J. Annas, M.A. Farley, N.E. Goldstein, R.M. Hamilton, G.N. Kay, D.B. Kramer, P.S. Mueller, L. Padeletti, L. Pozuelo, M.H. Schoenfeld, P.E. Vardas, D.L. Wiegand, R. Zellner, American College of Cardiology, American Geriatrics Society, American Academy of Hospice and Palliative Medicine, American Heart Association, European Heart Rhythm Association, Hospice and Palliative Nurses Association, HRS Expert Consensus Statement on the Management of Cardiovascular Implantable Electronic Devices (CIEDs) in patients nearing end of life or requesting withdrawal of therapy, *Heart Rhythm* 7 (2010) 1008–1026.
- [78] L. Padeletti, D.O. Arnar, L. Boncinelli, J. Brachman, J.A. Camm, J.C. Daubert, S.K. Hassam, L. Deliens, M. Glikson, D. Hayes, C. Israel, R. Lampert, T. Lobban, P. Raatikainen, G. Siegal, P. Vardas, Reviewers, P. Kirchhof, R. Becker, F. Cosio, P. Loh, S. Cobbe, A. Grace, J. Morgan, European Heart Rhythm Association; Heart Rhythm Society, EHRA Expert Consensus Statement on the management of cardiovascular implantable electronic devices in patients nearing end of life or requesting withdrawal of therapy, *Europace* 12 (2010) 1480–1489.

- [79] P. Thokala, H. Baalbaki, A. Brennan, A. Pandor, J.W. Stevens, T. Gomersall, J. Wang, A. Bakhai, A. Al-Mohammad, J. Cleland, M.R. Cowie, R. Wong, Telemonitoring after discharge from hospital with heart failure: cost-effectiveness modelling of alternative service designs, *BMJ Open* 3 (2013) e003250.
- [80] M.H. van der Wal, D.J. van Veldhuisen, N.J. Veeger, F.H. Rutten, T. Jaarsma, Compliance with non-pharmacological recommendations and outcomes in heart failure patients, *Eur. Heart J.* 31 (2010) 1486–1493.
- [81] R. Eschalier, F. Jean, B. Pereira, S. Monzy, C. Vorilhon, V. Mactoux, B. Citron, V. Sapin, P. Motreff, J.R. Lussan, Is there benefit in optimising heart failure treatment in over-80 year-old patients? (HF-80 study): study protocol for a randomized controlled trial, *Trials* 13 (2012) 25.
- [82] L.W. Stevenson, A.S. Hellkamp, C.V. Leier, G. Sopko, T. Koelling, J.W. Warnica, W.T. Abraham, E.K. Kasper, J.G. Rogers, R.M. Califf, E.E. Schramm, C.M. O'Connor, Changing preferences for survival after hospitalization with advanced heart failure, *J. Am. Coll. Cardiol.* 52 (2008) 1702–1708.
- [83] F. Formiga, D. Chivite, C. Ortega, S. Casas, J.M. Ramón, R. Pujol, End-of-life preferences in elderly patients admitted for heart failure, *QJM* 97 (2004) 803–808.
- [84] S. Dev, R.M. Clare, G.M. Felker, M. Fiuzat, L. Warner Stevenson, C.M. O'Connor, Link between decisions regarding resuscitation and preferences for quality of life with heart failure, *Eur. J. Heart Fail.* 14 (2012) 45–53.
- [85] M.R. Echols, W. Jiang, Clinical trial evidence for treatment of depression in heart failure, *Heart Fail. Clin.* 7 (2011) 81–88.
- [86] L. Pani, S. Pecorelli, G. Rosano, S.D. Anker, A. Peracino, L. Fragonese, K. Prasad, G. Rasi, Steps forward in regulatory pathways for acute and chronic heart failure, *ESC Heart Fail.* 17 (2015) 3–8.